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EXAMINER

NGUYEN, QUANG

ART UNIT

PAPER NUMBER

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

DETAILED ACTION

Applicant's amendment filed on 12/13/06 was entered.

Claims 1-21 are pending in the present application.

Claims 10-21 were withdrawn from further consideration because they are directed to non-elected invention.

Accordingly, amended claims 1-9 are examined on the merits herein.

Response to Amendment

The rejection under 35 USC 101 because the claimed invention is directed to non-statutory subject matter was withdrawn in light of Applicant's amendment.

The rejection of claims 2-3 and 5 under 35 U.S.C. 103(a) as being unpatentable over Klippel et al. (Mol. Cell. Biol. 14:2675-2685, 1994) in view of Kapeller et al. (BioEssays 16:565-576, 1994), Varticovski et al. (Mol. Cell. Biol. 11:1107-1113, 1991) and Aronheim et al. (Cell 78:949-861, 1994) and further in view of Eichner et al. (US 5,665,567) was withdrawn in light of Applicant's arguments of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hu et al. (Science 268:100-102, 1995) in view of Kapeller et al. (BioEssays 16:565-576, 1994), Varticovski et al. (Mol. Cell. Biol. 11:1107-1113, 1991) and Aronheim et al. (Cell 78:949-861, 1994) for the same reasons already set forth in the Office Action mailed on 2/28/06 (pages 4-6). ***The same rejection is restated below.***

Hu et al disclose the p110* construct which comprises DNA encoding the p110 subunit of PI 3-kinase and the iSH2 portion of the p85 subunit that is attached to the NH2 terminus of p110 via a glycine-kinker (see Figure 1). The encoded protein is a constitutively active form of PI 3-kinase (see entire document). Hu et al further teach NIH 3T3 cells and *Xenopus laevis* oocytes recombinantly expressing p110* that induces transcription from the *fos* promoter and Ras-dependent oocyte maturation, respectively (see at least the abstract).

Hu et al do not teach specifically a construct further comprising a DNA encoding a membrane targeting sequence.

At the effective filing date of the present application, Kapeller et al already taught that localization of PI 3-kinase to the plasma membrane brings the enzyme into closer contact with its substrates, (e.g., phosphatidylinositol (4,5) bis-phosphate to generate phosphatidylinositol (3,4,5) triphosphate), and the lipid products of PI 3-kinase are essential for mediating various cellular effects such as cellular growth, transformation as well as cellular differentiation (at least page 571, columns 1 and 2; and Figure 4). Varticovski et al also taught that PI 3-kinase must be localized to a plasma membrane to work efficiently (see abstract and page 112, left hand column). Aronheim et al taught methods for localizing proteins to membranes by addition of amino acid sequences that contain signals for myristoylation, farnesylation, and palmitoylation (see the entire document).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time the invention was made to modify the p110* construct of Hu et al by further adding DNA encoding membrane localization sequences in light of the teachings of Kapeller et al., Varticovski et al and Aronheim et al.

An ordinary skilled artisan would have been motivated to carry out the above modification to enhance the cellular responses or processes induced by PI 3-kinase because the localization of PI 3-kinase to the plasma membrane brings the enzyme into closer contact with its substrates, (e.g., phosphatidylinositol (4,5) bis-phosphate to generate phosphatidylinositol (3,4,5) triphosphate), and the lipid products of PI 3-kinase are essential for mediating various cellular effects such as cellular growth, transformation as well as cellular differentiation as taught by Kapeller et al and/or that PI

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3-kinase must be localized to a plasma membrane to work efficiently as taught by Varticovski et al.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings Hu et al., Kapeller et al., Varticovski et al and Aronheim et al, coupled with a high level of skill of an ordinary artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Response to Arguments

Applicants' arguments with respect the above rejection in the Amendment filed on 12/13/06 (pages 8-11) have been fully considered but they are respectfully not found persuasive.

1. Applicants argue that Hu actually teaches away from the instant invention, thus one of ordinary skill in the art would not have been motivated to combine the disclosures of Hu, Kapeller, Varticovski and Aronheim. Applicants argue that while each of Kapeller, Varticovski, and Aronheim discuss the importance of membrane localization for the *in vivo* activation of certain signaling proteins (e.g., wild-type PI 3-kinases and Raf-1), Hu discloses that the "only way" to activate PI 3-kinase required the use of tyrosine kinases (page 102, middle column, first full paragraph) and in his teachings, Hu expressed in cells a construct that was constitutively active in a growth factor-independent manner. By Hu's use of the limiting phrases "only way" in relation to activation and "required" in relation to tyrosine kinase, Hu was not open to other modes

of activation such as “myristoylation” as suggested by Varticovski or GTP-bound Ras as suggested by Aronheim.

It is initially noted that the instant claims are not limited to constitutively activated mutants, but also read on p110 subunit of a wild type PI 3-kinase or a non-constitutive active PI 3-kinase given the breadth of the claims. Given that the claims encompass non-constitutively activated p110*, one clearly would be motivated **to localize a wild type PI 3-kinase to the cell membrane for its activation and to be near to its substrates** as taught by Kapeller et al. and Varticovski et al., and this is also consistent with the teachings of Hu et al. Additionally, the statement “Until now it has not been possible to examine the action of PI-3 kinase directly, because the only way to activate PI-3 kinase required the use of tyrosine kinases that bind, phosphorylate, and localize PI-3 kinase. Here, we expressed in cells a PI-3 kinase that was constitutively active in a growth factor-independent manner...” (page 102, middle column, first full paragraph) merely indicates that **should an ordinary skilled artisan wish to examine the action of PI-3 kinase directly or in a growth factor-independent manner, then one should use the constitutively active PI –3 kinase of Hu et al.** However, the statement does not indicate or suggest an ordinary skilled artisan should not further modify the constitutively active PI-3 kinase in any shape or form (including the addition of a cell membrane targeting sequence) or using the constitutively active PI-3 kinase under any other circumstances, for example under growth factor exposure. In fact, Hu et al stated clearly that “Our approach should be useful for further studies elucidating how PI-3 kinase triggers this pathway and how this mechanism influences other cellular

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responses that are activated after growth factor exposure" (page 102, middle column; last sentence of second paragraph).

Even if the claims were limited to a mutated constitutively active p110* construct, an ordinary skilled artisan in the art would still be motivated to localize the encoded mutant to the cell membranes where its substrates are located, in order to achieve optimal production of its phosphorylated lipid products and maximal physiological responses mediated by these lipid products. With regards to the regulation of PI 3-kinase activity, Kapeller et al. teaches that the recruitment of PI 3-kinase to the plasma membrane drives the enzyme closer to its substrates, and this change in subcellular location may partially account for the activation of PI 3-kinase that is observed *in vivo* (column 1, lines 3-10, page 571). Kapeller et al. also noted the importance of recruiting oncogene-associated PI 3-kinase to the plasma membrane where the substrates for PI 3-kinase are located, because the *abl* mutant lacking the amino-terminal myristylation sequence fails to recruit associated PI 3-kinase to the plasma membrane to generate lipid products of PI 3-kinase, and in the absence of generated PI 3-kinase lipid products, mitogenic and transformation effects are not elicited (column 2, lines 7-27, page 571). Since Hu et al. already disclosed a constitutively active PI 3-kinase, arguments related to modes of activation required for the enzyme activation are not relevant. The main issue still is that although Hu et al. produced an enzyme which is constitutively active, they did nothing to alter the localization of the lipid substrates of the enzyme, and an ordinary skilled artisan in the art would still be motivated to localize the enzyme

at the cell membrane where the substrates are located as taught by the prior art in order to obtain a higher yield of phosphorylated lipid products and optimal effects mediated by the generated phosphorylated lipid products.

2. Applicants further argue that Kapeller, Varticovski and Aronheim teach away from the claimed invention by disclosing factors, in addition to membrane localization, that are not found in the present invention but that are required for PI 3-kinase activity. Particularly, Kapeller teaches away from the claimed polynucleotide fusion constructs by disclosing that other functional domains of p85, which are not components of the claimed polynucleotide fusion constructs may be important for protein-protein interactions and may be required for PI 3-kinase activity (e.g., SH2 and SH3 domains of p85). Varticovski and Aronheim do not directly address the teaching away by Kapeller, and neither teaches that membrane localization of a PI 3-kinase fusion construct with or without a membrane targeting domain, such as that of the claimed polynucleotide fusion constructs, will result in a catalytically active PI 3-kinase. In fact, Aronheim teaches the opposite, stating that localization to the plasma membrane alone may not be sufficient to produce a catalytically active PI 3-kinase, and that activation of PI 3-kinase may involve more complex mechanisms, including conformational changes, tyrosine phosphorylation and dephosphorylation of autophosphorylated serine/threonine sites on p110, and the contribution of these mechanisms to PI 3-kinase activation *in vivo* is not known. The combination of Kapeller, Varticovski and Aronheim not only teach away from the Applicant's claimed

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invention, but fail to suggest or provide a reasonable expectation of success that the Applicant's PI 3-kinase fusion constructs, regardless of the presence of a membrane targeting domain, would encode an active PI 3-kinase.

It is initially noted that the above rejection is under 35 U.S.C. 103(a), and therefore none of the cited references has to teach every limitation of the claims. The above arguments are not persuasive because Hu et al. already disclosed a modified constitutively active enzyme (not wild type) that does not require any other protein-protein interactions or any other factors. **Having produced a constitutively active enzyme, it would have been obvious for an ordinary skilled artisan to optimize its activity by co-localizing the enzyme with its substrates as taught by the prior art.**

Furthermore, the instant claims are not limited to constitutively active constructs, but also encompass wild type, non-constitutively active constructs **whose encoded enzymes need to be located at least to the cell membrane for activation** and to be near to the substrate in order to obtain a higher yield of phosphorylated lipid products and maximal physiological effects mediated by the generated phosphorylated lipid products, **regardless of the exact mechanisms involved in the activation of PI 3-kinase**. This is also supported by the statement of Hu et al. "Until now it has not been possible to examine the action of PI-3 kinase directly, **because the only way to activate PI-3 kinase required the use of tyrosine kinases that bind, phosphorylate, and localize PI-3 kinase**." (page 102, middle column, first full paragraph).

As stated previously, there was a reasonable expectation of success to modify the kinase of Hu et al. as set forth above so that it would be localized at the cell

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membrane to enhance the cellular responses or processes induced by PI 3-kinase because the localization of PI 3-kinase to the plasma membrane brings the enzyme into closer contact with its substrates, (e.g., phosphatidylinositol (4,5) bisphosphate to generate phosphatidylinositol (3,4,5) triphosphate), and the lipid products of PI 3-kinase are essential for mediating various cellular effects such as cellular growth, transformation as well as cellular differentiation as taught by Kapeller et al and/or that PI 3-kinase must be localized to a plasma membrane to work efficiently as taught by Varticovski et al. Applicants have not presented any evidence which would suggest otherwise.

Accordingly, claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hu et al. (Science 268:100-102, 1995) in view of Kapeller et al. (BioEssays 16:565-576, 1994), Varticovski et al. (Mol. Cell. Biol. 11:1107-1113, 1991) and Aronheim et al. (Cell 78:949-861, 1994) for the same reasons already set forth above.

Claims 1, 4 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klippel et al. (Mol. Cell. Biol. 14:2675-2685, 1994) in view of Kapeller et al. (BioEssays 16:565-576, 1994), Varticovski et al. (Mol. Cell. Biol. 11:1107-1113, 1991) and Aronheim et al. (Cell 78:949-861, 1994) for the same reasons already set forth in the Office Action mailed on 2/28/06 (pages 6-8). ***The same rejection is restated below.***

Klippel et al disclose constructs encoding the full-length p110 and p85 subunits of PI 3-kinase as well as their fragments, including the iSH2 portion of the p85 subunit (see Figure 1). Klippel et al further demonstrated that the complex containing either recombinant full length p85 or the iSH2-2 containing p85 fragments with the recombinant full length p110 exhibits PI 3-kinase activity in COS cells co-expressing these recombinant constructs (page 2679, left hand column, last paragraph continues to first paragraph of right hand column and Figure 4).

Klippel et al do not teach specifically any recombinant construct comprising a DNA encoding a membrane targeting sequence.

At the effective filing date of the present application, Kapeller et al already taught that localization of PI 3-kinase to the plasma membrane brings the enzyme into closer contact with its substrates, (e.g., phosphatidylinositol (4,5) bis-phosphate to generate phosphatidylinositol (3,4,5) triphosphate), and the lipid products of PI 3-kinase are essential for mediating various cellular effects such as cellular growth, transformation as well as cellular differentiation (at least page 571, columns 1 and 2; and Figure 4). Varticovski et al also taught that PI 3-kinase must be localized to a plasma membrane to work efficiently (see abstract and page 112, left hand column). Aronheim et al taught methods for localizing proteins to membranes by addition of amino acid sequences that contain signals for myristoylation, farnesylation, and palmitoylation (see the entire document).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time the invention was made to modify the constructs of Klippel et al by further adding DNA

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encoding membrane localization sequences in light of the teachings of Kapeller et al., Varticovski et al and Aronheim et al.

An ordinary skilled artisan would have been motivated to carry out the above modification to enhance the cellular responses or processes induced by PI 3-kinase because the localization of PI 3-kinase to the plasma membrane brings the enzyme into closer contact with its substrates, (e.g., phosphatidylinositol (4,5) bis-phosphate to generate phosphatidylinositol (3,4,5) triphosphate), and the lipid products of PI 3-kinase are essential for mediating various cellular effects such as cellular growth, transformation as well as cellular differentiation as taught by Kapeller et al and/or that PI 3-kinase must be localized to a plasma membrane to work efficiently as taught by Varticovski et al.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings Klippel et al., Kapeller et al., Varticovski et al and Aronheim et al, coupled with a high level of skill of an ordinary artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Response to Arguments

Applicants' arguments with respect the above rejection in the Amendment filed on 12/13/06 (pages 12-14) have been fully considered but they are respectfully not found persuasive.

1. Applicants argue that at the time of the invention, an ordinary skilled artisan would not equate the *in vivo* co-expression of PI 3-kinase subunits, which assumes conformation that allows them to specifically bind to one another, with that which occurs "when the two subunits are co-expressed (end to end) as a fusion protein". Applicants further argue that Klippel discloses that the binding of p85 to p110 is "necessary, but not sufficient for PI 3-kinase activity" and the teachings of Klippel do not teach that association *in vitro* of the two subunits produced separately produce an active enzyme. Therefore, an ordinary skilled artisan would appreciate the importance of "conformational changes" following the binding of p85 to p110 to PI 3-kinase activation. In the absence of actual testing, an ordinary skilled artisan would not have a reasonable expectation that p85 and p110 subunits tethered together by a glycine linker would have the appropriate spatial and conformational relationships to allow them to bind together to form a p85/p110 complex or that the resulting complex would have PI 3-kinase activity because (1) the glycine linker could prevent the conformational changes otherwise induced by the binding of p85 to p110 and otherwise required for proper folding of the p110 catalytic domain, and/or (2) the glycine linker could constrain the p85 and p110 subunits from properly interacting with other proteins that were believed to be necessary for, but not sufficient to activate PI 3-kinase. Accordingly, Klippel teaches away from any expectation that the claimed polynucleotide fusion constructs would encode a protein forming a p85/p110 complex having PI 3-kinase activity.

Firstly, it is noted that the instant rejected claims are not directed to an isolated polynucleotide sequence encoding a fusion protein containing p85 and p110 subunits of PI 3-kinase or any glycine linker or that the encoded protein has any PI 3-kinase activity. It is apparent that Applicants read the specification into the claims.

Secondly, with respect to Applicant's argument that Klippel et al. only teach that the association of the p110 and p85 subunits is necessary but not sufficient to produce PI 3-kinase activity, and other mechanisms including conformational changes induced by the p110-p85 complex formation may be involved in the PI 3-kinase activation, this argument is not persuasive. This is only partially true. Klippel et al. teach that association *in vitro* of the two subunits produced separately did not produce an active enzyme. However, Klippel et al. continue on to indicate that this problem is overcome when the two subunits are co-expressed and allowed to associate *in vivo* (p. 2682, first paragraph and page 2680, the section entitled "The immediate N-terminus of p110 is essential for interaction with the 85-kDa subunit and enzyme activity"). It is also noted that Klippel et al. discussed mechanisms potentially involved in the activation of PI 3-kinase in an attempt to explain the lack of PI 3-kinase activity for p85-p110 complex in a cell free system. However, all of them are possibilities and they are yet proven, including the presence of an unidentified factor in a cell that could recognize interactive domains of the PI 3-kinase subunits and could lead to a stimulatory conformational change (column 2, page 2683).

Thirdly, since Klippel et al were already successful in *in vivo* co-expression of PI 3-kinase subunits to produce an active enzyme, then why wouldn't an ordinary skilled artisan be motivated to modify the constructs of Klippel et al by further adding DNA encoding membrane localization sequences (nothing to do with making any fusion protein between p110 and p85) to enhance the cellular responses or processes induced by the reconstituted and active PI 3-kinase subunits *in vivo*? This is because the localization of PI 3-kinase to the plasma membrane brings the enzyme into closer contact with its substrates, (e.g., phosphatidylinositol (4,5) bis-phosphate to generate phosphatidylinositol (3,4,5) triphosphate), and the lipid products of PI 3-kinase are essential for mediating various cellular effects such as cellular growth, transformation as well as cellular differentiation as taught by Kappeller et al and/or that PI 3-kinase must be localized to a plasma membrane to work efficiently as taught by Varticovski et al.

2. With respect to Applicant's argument that Kappeller et al. teach that other functional domains of the p85 protein are important in regulating enzyme activity, this argument is not persuasive because Klippel et al. (1994) present a model in which the other domains of the p85 subunit are not attached to the p110 subunit at all (Figure 7). Kappeller et al. indicate that the other domains of p85 are probably important for interacting with other proteins in the cell, such as receptors, but this does not indicate that these domains are required for PI 3-kinase enzymatic activity.

3. With respect to Applicant's argument that Aronheim et al. teach that membrane localization might not be sufficient for enzyme activation, this argument is not persuasive. The disclosure of Aronheim et al. is limited to a review of literature published before the 1994 Klippel et al. article. Klippel et al. showed that co-expression of the iSH2 fragment and p110 *in vivo* is sufficient to produce an active enzyme (i.e. the enzyme was isolated from cells and fed labeled substrate). **The purpose of attaching the membrane localization signal is to localize the enzyme with its substrate at the cell membrane, which was expected to increase the amount of lipid product generated.**

4. With respect to Applicant's argument that the combined disclosures of Klippel et al., Kapeller et al., Varticovski et al., and Aronheim et al. is an "obvious to try" rejection, this argument is not persuasive. As stated previously, there was a reasonable expectation of success that modifying the constructs of Klippel et al. by further adding DNA encoding membrane localization sequences to the constructs (nothing to do with making any fusion protein between p110 and p85) **to enhance the cellular responses or processes induced by the reconstituted and active PI 3-kinase subunits *in vivo***, particularly Klippel et al were already successful in *in vivo* co-expression of PI 3-kinase subunits to produce an active enzyme.

Accordingly, claims 1, 4 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klippel et al. (Mol. Cell. Biol. 14:2675-2685, 1994) in view of Kapeller et al. (BioEssays 16:565-576, 1994), Varticovski et al. (Mol. Cell. Biol. 11:1107-1113,

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1991) and Aronheim et al. (Cell 78:949-861, 1994) for the same reasons set forth above.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,300,111 B1 in view of Kapeller et al. (BioEssays 16:565-576, 1994), Varticovski et al. (Mol. Cell. Biol. 11:1107-1113, 1991) and Aronheim et al. (Cell 78:949-861, 1994) for the same reasons already set forth in the Office Action mailed on 2/28/06 (pages 10-12). ***The same rejection is restated below.***

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(I)(1) and § 706.02(I)(2).

U.S. Patent No. 6,300,111 B1 teaches the preparation of an expression vector comprising a DNA sequence encoding a constitutively active phosphatidylinositol 3-kinase polypeptide, wherein the polypeptide comprises a p85 subunit iSH2 domain sequence or a conservatively modified variant thereof linked at the carboxy-terminus by a linker to the amino-terminus of a p110 subunit or a conservatively modified variant thereof and a cell containing the expression vector (see the entire document, especially claims 1-4)

However, the U.S. Patent No. 6,300,111 B1 does not teach that the expression vector further comprises a nucleotide sequence comprising a sequence encoding a cell membrane targeting sequence at the 5' end or 3' end of the DNA sequence encoding a constitutively active phosphatidylinositol 3-kinase polypeptide.

At the effective filing date of the present application, Kapeller et al already taught that localization of PI 3-kinase to the plasma membrane brings the enzyme into closer contact with its substrates, (e.g., phosphatidylinositol (4,5) bis-phosphate to generate phosphatidylinositol (3,4,5) triphosphate), and the lipid products of PI 3-kinase are essential for mediating various cellular effects such as cellular growth, transformation as well as cellular differentiation (at least page 571, columns 1 and 2; and Figure 4). Varticovski et al also taught that PI 3-kinase must be localized to a plasma membrane to work efficiently (see abstract and page 112, left hand column). Aronheim et al taught methods for localizing proteins to membranes by addition of amino acid sequences that contain signals for myristoylation, farnesylation, and palmitoylation (see the entire document).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time the invention was made to modify the expression vector construct of U.S. Patent No. 6,300,111 B1 by further adding DNA encoding membrane localization sequences to the 5' end or 3' end of the DNA sequence encoding a constitutively active phosphatidylinositol 3-kinase polypeptide in light of the teachings of Kapeller et al., Varticovski et al and Aronheim et al.

An ordinary skilled artisan would have been motivated to carry out the above modification to enhance the cellular responses or processes induced by PI 3-kinase because the localization of PI 3-kinase to the plasma membrane brings the enzyme into closer contact with its substrates, (e.g., phosphatidylinositol (4,5) bis-phosphate to generate phosphatidylinositol (3,4,5) triphosphate), and the lipid products of PI 3-kinase are essential for mediating various cellular effects such as cellular growth, transformation as well as cellular differentiation as taught by Kapeller et al and/or that PI 3-kinase must be localized to a plasma membrane to work efficiently as taught by Varticovski et al.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings U.S. Patent No. 6,300,111 B1, Kapeller et al., Varticovski et al and Aronheim et al, coupled with a high level of skill of an ordinary artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Response to Arguments

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Applicants' arguments with respect the above rejection in the Amendment filed on 12/13/06 (pages 16-18) have been fully considered but they are respectfully not found persuasive.

Applicants argue basically that Kapeller, Varticovski and Aronheim teach away from the claimed invention by disclosing factors, in addition to membrane localization, that are not found in the present invention but that are required for PI 3-kinase activity. Applicants presented the same "teaching away" arguments as those presented for the rejection of claims 1-9 under 35 U.S.C. 103(a) as being unpatentable over Hu et al. (Science 268:100-102, 1995) in view of Kapeller et al. (BioEssays 16:565-576, 1994), Varticovski et al. (Mol. Cell. Biol. 11:1107-1113, 1991) and Aronheim et al. (Cell 78:949-861, 1994) above.

It is initially noted that Applicants ignored completely the teachings in the issued U.S. Patent No. 6,300,111 B1.

With respect to the alleged teaching away by Kapeller, Varticovski and Aronheim, U.S. Patent No. 6,300,111 B1 already taught the preparation of an expression vector comprising a DNA sequence encoding a constitutively active phosphatidylinositol 3-kinase polypeptide, wherein the polypeptide comprises a p85 subunit iSH2 domain sequence or a conservatively modified variant thereof linked at the carboxy-terminus by a linker to the amino-terminus of a p110 subunit or a conservatively modified variant thereof that does not require any other protein-protein interactions or any other factors. Having produced a constitutively active enzyme, it would have been obvious for an ordinary skilled artisan to optimize its

activity by co-localizing the enzyme with its substrates as taught by the prior art.

Furthermore, the instant claims are not limited to constitutively active constructs, but also encompass wild type, non-constitutively active constructs **whose encoded enzymes need to be located at least to the cell membrane for activation** and to be near to the substrate in order to obtain a higher yield of phosphorylated lipid products and maximal physiological effects mediated by the generated phosphorylated lipid products, **regardless of the exact mechanisms involved in the activation of PI 3-kinase.**

As stated previously, there was a reasonable expectation of success to modify the expression vector construct of U.S. Patent No. 6,300,111 B1 by further adding DNA encoding membrane localization sequences to the 5' end or 3' end of the DNA sequence encoding a constitutively active phosphatidylinositol 3-kinase polypeptide so that the encoded modified enzyme would be localized at the cell membrane to enhance the cellular responses or processes induced by PI 3-kinase because **the localization of PI 3-kinase to the plasma membrane brings the enzyme into closer contact with its substrates,** (e.g., phosphatidylinositol (4,5) bis-phosphate to generate phosphatidylinositol (3,4,5) triphosphate), and the lipid products of PI 3-kinase are essential for mediating various cellular effects such as cellular growth, transformation as well as cellular differentiation as taught by Kapeller et al and/or **that PI 3-kinase must be localized to a plasma membrane to work efficiently as taught by Varticovski et al.** Applicants have not presented any evidence which would suggest otherwise.

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Accordingly, claims 1-9 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,300,111 B1 in view of Kapeller et al. (BioEssays 16:565-576, 1994), Varticovski et al. (Mol. Cell. Biol. 11:1107-1113, 1991) and Aronheim et al. (Cell 78:949-861, 1994) for the same reasons set forth above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,300,111 B1 in view of Kapeller et al. (BioEssays 16:565-576, 1994), Varticovski et al. (Mol. Cell. Biol. 11:1107-1113, 1991) and Aronheim et al. (Cell 78:949-861, 1994) for the same reasons

already set forth in the Office Action mailed on 2/28/06 (pages 13-15). ***The same rejection is restated below.***

The instant claims are directed to a polynucleotide sequence comprising: (a) a first nucleotide sequence comprising a sequence encoding the p110 subunit of PI 3-kinase protein or its derivative or mutant having a single or multiple nucleotide substitution, deletion or addition, and (b) a second nucleotide sequence comprising a sequence encoding a cell membrane targeting sequence, wherein said second nucleotide sequence being attached to the 5' or 3' end of said first nucleotide sequence; and a cell transformed with the polynucleotide sequence.

Claims 1-4 of U.S. Patent No. 6,300,111 B1 are drawn to an expression vector comprising a DNA sequence encoding a constitutively active phosphatidylinositol 3-kinase polypeptide, wherein the polypeptide comprises a p85 subunit iSH2 domain sequence or a conservatively modified variant thereof linked at the carboxy-terminus by a linker to the amino-terminus of a p110 subunit or a conservatively modified variant thereof and a cell containing the expression vector.

The claims of the present application differ from the claims of the U.S. Patent No. 6,300,111 B1 in reciting that the polynucleotide sequence further comprises a nucleotide sequence comprising a sequence encoding a cell membrane targeting sequence.

At the effective filing date of the present application, Kapeller et al already taught that localization of PI 3-kinase to the plasma membrane brings the enzyme into closer contact with its substrates, (e.g., phosphatidylinositol (4,5) bis-phosphate to generate

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phosphatidylinositol (3,4,5) triphosphate), and the lipid products of PI 3-kinase are essential for mediating various cellular effects such as cellular growth, transformation as well as cellular differentiation (at least page 571, columns 1 and 2; and Figure 4). Varticovski et al also taught that PI 3-kinase must be localized to a plasma membrane to work efficiently (see abstract and page 112, left hand column). Aronheim et al taught methods for localizing proteins to membranes by addition of amino acid sequences that contain signals for myristoylation, farnesylation, and palmitoylation (see the entire document).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time the invention was made to modify the expression vector construct of U.S. Patent No. 6,300,111 B1 by further adding DNA encoding membrane localization sequences to the 5' end or 3' end of the DNA sequence encoding a constitutively active phosphatidylinositol 3-kinase polypeptide in light of the teachings of Kapeller et al., Varticovski et al and Aronheim et al.

An ordinary skilled artisan would have been motivated to carry out the above modification to enhance the cellular responses or processes induced by PI 3-kinase because the localization of PI 3-kinase to the plasma membrane brings the enzyme into closer contact with its substrates, (e.g., phosphatidylinositol (4,5) bis-phosphate to generate phosphatidylinositol (3,4,5) triphosphate), and the lipid products of PI 3-kinase are essential for mediating various cellular effects such as cellular growth, transformation as well as cellular differentiation as taught by Kapeller et al and/or that PI

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3-kinase must be localized to a plasma membrane to work efficiently as taught by Varticovski et al.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings U.S. Patent No. 6,300,111 B1, Kapeller et al., Varticovski et al and Aronheim et al, coupled with a high level of skill of an ordinary artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Response to Arguments

Applicants' arguments with respect the above rejection in the Amendment filed on 12/13/06 (pages 16-18) have been fully considered but they are respectfully not found persuasive.

Applicants presented the same arguments as those in response to the rejection of claims 1-9 under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,300,111 B1 in view of Kapeller et al. (BioEssays 16:565-576, 1994), Varticovski et al. (Mol. Cell. Biol. 11:1107-1113, 1991) and Aronheim et al. (Cell 78:949-861, 1994). Please refer to the same Examiner's responses above.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It

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also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.


QUANG NGUYEN, PH.D.
PRIMARY EXAMINER